Claims

1. A method for identifying a subject at risk of developing a tumor characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule comprising

determining a level of methylation of a CpG island containing TMS1 nucleic acid molecule in a biological sample from a subject, and

comparing the level of methylation of the CpG island containing TMS1 nucleic acid molecule in the biological sample to a control

wherein the CpG island containing TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4 and which code for a native TMS1 polypeptide, and

(b) complements of (a), and

wherein an increase in the level of methylation of the CpG island containing TMS1 nucleic acid molecule in the biological sample compared to the control identifies a subject at risk of developing the tumor.

2. The method of claim 1, wherein the level of methylation is determined using a technique selected from the group consisting of methylation sensitive restriction analysis, methylation specific polymerase chain reaction (MSP), sequencing of bisulfite modified DNA, methylation-sensitive single nucleotide primer extension (Ms-SNuPE), and combined bisulfite restriction analysis (COBRA).

3. The method of claim 1, wherein the biological sample is breast tissue.

4. The method of claim 1, wherein the control comprises a normal tissue from a normal subject.

5. A method for determining a risk of developing a disorder characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule comprising

measuring a level of an expression product of a CpG island containing TMS1 nucleic acid molecule, by contacting a biological sample isolated from a subject with an agent that selectively binds to a target expression product selected from the group consisting of

(a) nucleic acid expression products which hybridize under stringent conditions to a complement of a molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:24 and which code for a native TMS1 polypeptide, and

(b) polypeptide expression products, and fragments thereof, of (a),

determining a level of interaction between the agent and the target expression product, and

comparing the level of interaction between the agent and the target expression product with a control.

6. The method of claim 5, wherein the control comprises a normal tissue from a normal subject.

7. The method of claim 5, wherein a decrease in the level of interaction between the agent and the target expression product in the biological sample compared to the control indicates a risk of developing the disorder.

8. The method of claim 5, wherein the disorder is cancer.

9. The method of claim 8, wherein the cancer is breast cancer.

10. The method of claim 5, wherein the agent is a nucleic acid molecule.

11. The method of claim 5, wherein the agent is a peptide.

12. The method of claim 11, wherein the peptide is an antibody or a fragment thereof.

13. A method for treating a subject at risk of developing a disorder characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule comprising

administering a demethylating agent to a subject in need of such treatment in an amount effective to maintain a normal level of methylation in a CpG island containing TMS1 nucleic acid molecule in a tissue of the subject,

wherein the CpG island containing TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO:4, and which code for a native TMS1 polypeptide, and

(b) complements of (a).

14. The method of claim 13, wherein the demethylating agent is administered to a tissue at risk of developing a tumor.

15. The method of claim 13, wherein the demethylating agent is an inhibitor of methyltransferase.

16. The method of claim 15, wherein the inhibitor of methyltransferase is selected from the group consisting of 5-azacytidine, 5-aza-2'deoxycytidine, 5, 6-dihydro-5-azacytidine, 5-fluorocytidine and 5-fluoro-2'deoxycytidine.

17. The method of claim 13, wherein the demethylating agent is conjugated to a nucleic acid molecule selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO: 1, and

(b) complements of (a).

18. The method of claim 13, wherein the disorder is cancer.

19. The method of claim 18, wherein the cancer is breast cancer.

20. The method of claim 13, further comprising first selecting a subject at risk of developing the disorder.

21. A method for treating a subject having or at risk of developing a disorder characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule comprising

administering a CARD containing molecule to a subject in need of such treatment in an amount effective to increase CARD polypeptide level in a tissue of the subject,

wherein the CARD containing molecule is selected from the group consisting of a CARD containing nucleic acid molecule or a CARD containing polypeptide.

22. The method of claim 21, wherein the CARD containing molecule is a TMS1 molecule.

23. The method of claim 22, wherein the TMS1 molecule is selected from the group consisting of a TMS1 nucleic acid molecule or a TMS1 polypeptide.

24. The method of claim 21, wherein the CARD containing nucleic acid molecule has an nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:9, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:24.

25. The method of claim 21, wherein the CARD containing polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:10, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

26. The method of claim 21, wherein the CARD containing molecule is administered to a tissue having or at risk of developing a tumor.

27. The method of claim 21, wherein the disorder is cancer.

28. The method of claim 27, wherein the cancer is breast cancer.

29. The method of claim 21, further comprising first selecting a subject having or at risk of developing the disorder.

30. A method for treating a subject having a disorder characterized by abnormally low levels of a TMS1 expression product comprising

administering a demethylating agent to a subject in need of such treatment in an amount effective to reduce a level of methylation in a CpG island containing TMS1 nucleic acid molecule in a cell of the subject,

wherein the CpG island containing TMS1 molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO:4, and which code for a native TMS1 polypeptide, and

(b) complements of (a).

31. The method of claim 30, wherein the demethylating agent is administered to a tissue at risk of developing a tumor.

32. The method of claim 30, wherein the demethylating agent is an inhibitor of methyltransferase.

33. The method of claim 32, wherein the inhibitor of methyltransferase is selected from the group consisting of 5-azacytidine, 5-aza-2'deoxycytidine, 5, 6-dihydro-5-azacytidine, 5-fluorocytidine and 5-fluoro-2'deoxycytidine.

34. The method of claim 30, wherein the demethylating agent is conjugated to a nucleic acid molecule selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO: 1, and

(b) complements of (a).

35. The method of claim 30, wherein the disorder is cancer.

36. The method of claim 35, wherein the cancer is breast cancer.

37. The method of claim 30, wherein the level of methylation in the CpG island containing TMS1 nucleic acid molecule is reduced compared to a pre-treatment level of methylation.

38. A method for treating a subject having or at risk of having a disorder characterized by abnormally low levels of a TMS1 expression product comprising

administering a CARD containing molecule to a subject in need of such treatment in an amount effective to increase CARD containing polypeptide level in a tissue of the subject,

wherein the CARD containing molecule is selected from the group consisting of a CARD containing nucleic acid molecule and CARD containing polypeptide.

39. The method of claim 38, wherein the CARD containing molecule is a TMS1 molecule.

40. The method of claim 39, wherein the TMS1 molecule is selected from the group consisting of TMS1 nucleic acid molecule and TMS1 polypeptide.

41. The method of claim 38, wherein the CARD containing nucleic acid molecule comprises an nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:9, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:24.

42. The method of claim 38, wherein the CARD containing polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:10, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

43. The method of claim 38, wherein the CARD containing molecule is administered to a tissue having or at risk of developing a tumor.

44. The method of claim 38, wherein the disorder is cancer.

45. The method of claim 44, wherein the cancer is breast cancer.

46. The method of claim 38, further comprising first selecting a subject having or at risk of developing the disorder.

47. A method for identifying a subject having cancer who is at risk of being non-responsive to an anti-cancer therapy comprising:

determining a level of methylation of a CpG island containing TMS1 nucleic acid molecule in a biological sample from a subject having cancer, and

comparing the level of methylation of the CpG island containing TMS1 nucleic acid molecule in the biological sample to a control,

wherein the CpG island containing TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO:4 and which code for a native TMS1 polypeptide, and

(b) complements of (a), and

wherein an increase in the level of methylation of the CpG island containing TMS1 nucleic acid molecule in the biological sample compared to the control identifies subject who is at risk of being non-responsive to an anti-cancer therapy.

48. The method of claim 47, wherein the level of methylation is determined using a technique selected from the group consisting of methylation sensitive restriction analysis, methylation specific polymerase chain reaction (MSP), sequencing of bisulfite modified DNA, methylation-sensitive single nucleotide primer extension (Ms-SNuPE), and combined bisulfite restriction analysis (COBRA).

49. The method of claim 47, wherein the cancer is breast cancer.

50. The method of claim 48, wherein the biological sample is a breast cancer tumor.

51. The method of claim 47, wherein the control is normal tissue from a normal subject.

52. The method of claim 51, wherein the control is normal tissue from the subject having cancer.

53. The method of claim 47, wherein the anti-cancer therapy is a DNA damaging anti-cancer therapy.

54. The method of claim 47, wherein the anti-cancer therapy is radiation therapy.

55. The method of claim 47, wherein the anti-cancer therapy is chemotherapy.

56. The method of claim 47, further comprising administering to the subject at risk of being non-responsive to an anti-cancer therapy, a demethylating agent and an anti-cancer therapy.

57. The method of claim 47, further comprising administering to the subject at risk of being non-responsive to an anti-cancer therapy, an anti-cancer therapy selected from the group consisting of biological response modifying therapy, immunotherapy, cancer vaccine therapy, hormone therapy and angiogenesis inhibiting therapy.

58. A method for treating a subject having a cancer comprising

administering a demethylating agent and an anti-cancer therapy to a subject in need of such treatment in an amount effective to treat the cancer,

wherein the cancer is selected from the group consisting of a cancer characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule, and a cancer characterized by an abnormally low levels of a TMS1 expression product

wherein the CpG island containing TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO:4, and which code for a native TMS1 polypeptide, and

(b) complements of (a).

59. The method of claim 58, wherein demethylating agent is administered prior to the anti-cancer therapy.

60. The method of claim 58, wherein the demethylated agent is administered in amount effective to sensitize the cancer to the anti-cancer therapy.

61. A method for treating a subject having a cancer comprising

administering a TMS1 molecule and an anti-cancer therapy to a subject in need of such treatment in an amount effective to treat the cancer,

wherein the cancer is selected from the group consisting of a cancer characterized by abnormal methylation of a CpG island containing TMS1 nucleic acid molecule, and a cancer characterized by an abnormally low levels of a TMS1 expression product

wherein the CpG island containing TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule comprising SEQ ID NO:4, and which code for a native TMS1 polypeptide, and

(b) complements of (a).

62. The method of claim 61, wherein the TMS1 molecule is administered prior to the anti-cancer therapy.

63. The method of claim 61, wherein the TMS1 molecule is administered in an amount effective to sensitize the cancer to the anti-cancer therapy.

64. The method of claim 61, wherein the TMS1 molecule is selected from the group consisting of a TMS1 nucleic acid molecule and a TMS1 polypeptide.

65. The method of claim 64, wherein the TMS1 nucleic acid molecule has an nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:24.

66. The method of claim 64, wherein the TMS1 polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

67. A method for treating a subject having a disorder characterized by abnormal cell proliferation, comprising

administering to a subject in need of such treatment a TMS1 molecule in an amount effective to increase TMS1 polypeptide level to an above normal level.

68. An isolated nucleic acid molecule, comprising

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule having a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO: 2, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:20, SEQ ID NO:22 and SEQ ID NO:24, and which code for a native TMS1 polypeptide,

(b) deletions, additions and substitutions of (a), which code for an apoptosis inducing polypeptide,

(c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) in codon sequence due to the degeneracy of the genetic code, and

(d) complements of (a), (b) or (c).

69. The isolated nucleic acid molecule of claim 68, wherein the isolated nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:20, SEQ ID NO:22, and SEQ ID NO:24.

70. The isolated nucleic acid molecule of claim 68, wherein the isolated nucleic acid molecule codes for a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

71. An isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:4.

72. An isolated nucleic acid molecule selected from the group consisting of

(a) a unique fragment of a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:1, and

(b) complements of (a)

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence from the sequence group consisting of

(1) sequences having the database accession numbers of Table 1, and

(2) complements of (1).

73. The isolated nucleic acid of claim 72, wherein the sequence of contiguous nucleotides is selected from the group consisting of:

(1) at least two contiguous nucleotides nonidentical to the sequence group,

(2) at least three contiguous nucleotides nonidentical to the sequence group,

(3) at least four contiguous nucleotides nonidentical to the sequence group,

(4) at least six contiguous nucleotides nonidentical to the sequence group,

(5) at least eight contiguous nucleotides nonidentical to the sequence group,

(6) at least ten contiguous nucleotides nonidentical to the sequence group.

74. The isolated nucleic acid molecule of claim 72 or 73, wherein the unique fragment has a size selected from the group consisting of at least: 8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20 nucleotides, 22 nucleotides, 24 nucleotides, 26

nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides and 200 nucleotides.

75. The isolated nucleic acid molecule of claim 72 or 73 wherein the unique fragment encodes a peptide which is a fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:25.

76. The isolated nucleic acid molecule of claim 74, wherein the unique fragment encodes a peptide which is a fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:25.

77. An expression vector comprising the isolated nucleic acid molecule of claims 68, 69 or 70, operably linked to a promoter.

78. An expression vector comprising the isolated nucleic acid molecule of claim 71, or a regulatory fragment thereof, operably linked to a reporter coding sequence.

79. The expression vector of claim 78, wherein the reporter coding sequence comprises a promoter.

80. An expression vector comprising the isolated nucleic acid molecule of 75, operably linked to a promoter.

81. An expression vector comprising the isolated nucleic acid molecule of claim 76, operably linked to a promoter.

82. A host cell transformed or transfected with the expression vector of claim 77.

83. A host cell transformed or transfected with the expression vector of claim 78, 79, 80 or 81.

84. An isolated polypeptide encoded by the isolated nucleic acid molecule of claim 68, wherein the isolated polypeptide is a native TMS1 polypeptide.

85. The isolated polypeptide of claim 84, wherein the isolated polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

86. An isolated peptide comprising a fragment of the isolated polypeptide of claim A18, of sufficient length to represent a sequence unique within the human genome and to identify a native TMS1 polypeptide.

87. The isolated peptide of claim 86, wherein the fragment is immunogenic.

88. The isolated peptide of claim 86, wherein the peptide comprises at least 6, 8, 9, 10, 11, 12, 14, 16, 18 or 20 contiguous amino acids having a sequence of a fragment of SEQ ID NO:3 or SEQ ID NO:25.

89. A composition comprising

an isolated agent that binds selectively to a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25, or to a fragment thereof.

90. The composition of claim 89, wherein the isolated agent is a peptide.

91. The composition of claim 92, wherein the peptide is an antibody, or a fragment thereof.

92. The composition of claim 91, wherein the antibody is a humanized antibody or a chimeric antibody.

93. The composition of claim 89, wherein the isolated agent is conjugated to a detectable label.

94. The composition of claim 93, wherein the detectable label is selected from the group consisting of a radioactive label, an enzyme, a biotin molecule, an avidin molecule or a fluorochrome.

95. A method for identifying a nucleic acid molecule transcriptionally down-regulated following methylation, comprising

overexpressing a methyltransferase molecule in a experimental cell, and

identifying a differentially expressed molecule which has a lower level of expression in the experimental cell than in a control.

96. The method of claim 95, wherein the DNA methyltransferase is a human DNA methyltransferase.

97. The method of claim 96, wherein the experimental cell is HMT.1E1.

98. The method of claim 95, wherein the control is an SV40 immortalized fibroblast cell line.

99. The method of claim 95, wherein the expression product is an mRNA.

100. The method of claim 95, wherein the differentially expressed molecule is identified using a technique selected from the group consisting of subtractive hybridization, differential display, representational difference analysis and cDNA microarray analysis.

101. A method for identifying a TMS1 polypeptide binding partner comprising

obtaining a binding assay result from a binding assay between a library member and a TMS1 polypeptide, and

comparing the binding assay result to a control binding assay result,

wherein a binding assay result that is greater than a control binding assay result indicates that the library member is a TMS1 polypeptide binding partner.

102. The method of claim 101, wherein the TMS1 polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25.

103. The method of claim 101, wherein the library member is derived from a natural source library.

104. The method of claim 103, wherein the TMS1 polypeptide binding partner is naturally occurring.

105. A method for identifying a TMS1 N-terminal polypeptide binding partner comprising

obtaining a binding assay result from a binding assay between a library member and a TMS1 N-terminal polypeptide, and

comparing the binding assay result to a control binding assay result,

wherein a binding assay result that is greater than a control binding assay result indicates that the library member is a TMS1 N-terminal polypeptide binding partner.

106. The method of claim 105, wherein the TMS1 N-terminal polypeptide binding partner has an amino acid sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:26.

107. The method of claim 105, wherein the TMS1 N-terminal polypeptide binding partner has an amino acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:21, SEQ ID NO:23 and SEQ ID NO:25, and the control binding assay result is obtained from a control binding assay between a library member and a polypeptide consisting of an amino acid sequence of SEQ ID NO:10.

108. The method of claim 105, wherein the library member is derived from a natural source library.

109. The method of claim 108, wherein the TMS1 polypeptide binding partner is naturally occurring.